REMARKS

The fees for filing the RCE and for a three month extension of time should be charged to Deposit Account No. 02-1818. Any fees that may be due in connection with filing this paper or with this application during its entire pendency may be charged to Deposit Account No. 02-1818. If a Petition for extension of time is required, this paper is to be considered such Petition, and any fee charged to Deposit Account No. 02-1818.

A Supplemental Information Disclosure Statement in connection with the filing of this RCE, was filed under separate cover on September 29, 2009.

Claims 1-6, 9, 12-16, 18 and 21-23 are pending. Claims 1, 13, 15 and 23 are amended to render it clear that bacteria are systemically administered, and then detected inside a subject to identify their location, which indicates the location of a wounded or inflamed tissue inside a subject. The claims also are amended to render it clear the method is a method for detecting inflamed or wounded tissues inside a subject, not a method for detecting or monitoring infection. Claims 3-5, 13 and 15, which are directed to non-elected species, are withdrawn. They are retained pending allowance of a generic claim. Applicant reserves the right to file continuing/divisional applications to non-elected, cancelled and unclaimed subject matter.

THE REJECTION OF CLAIMS 1, 9 AND 23 UNDER 35 U.S.C. §102

Rejection of Claims 1, 9 and 23 under 35 U.S.C. §102(b)

Claims 1, 9 and 23 are rejected under 35 U.S.C. 102(b) as anticipated by Hamblin *et al.* (2002) *Photochem. Photobiol.* 75:51-57 for reasons made of record and because Hamblin allegedly administers bacteria into the wounds by "subcutaneous, topical, or intradermal administration." The Examiner urges that Hamblin discloses "administration and detection in wounds" within a subject because the wounds are at least 8 x 12.5 x 5 mm (page 52, second column, last), thus, the bacterium was administered and detected "within" the subject. This rejection respectfully is traversed.

Relevant Law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir, 1990), *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990), *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the

invention." *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). It is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference. *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

"Rejections under 35 U.S.C. §102 are proper only when the claimed subject matter is identically disclosed or described in the 'prior art' . . . the [r]eference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings in the cited references. Such picking and choosing may be entirely proper when making a rejection of a §103, obviousness rejection, where the applicant must be afforded an opportunity to rebut with objective evidence any inference of obviousness which may arise from the *similarity* of the subject matter which he claims to the prior art, but it has no place in the making of a §102, anticipation rejection." (Emphasis in original). *In re Arkey, Eardly, and Long*, 455 F.2d 586, 172 USPQ 524 (CCPA, 1972).

The Claims

Claim 1 is directed to a method for **detecting wounded or inflamed tissue** inside of a subject. To effect detection, a bacterium is systemically administered. The bacterium is detectable in the subject; the bacterium replicates in the subject; the bacterium is not pathogenic to the subject and is recognized by the immune system of the subject; the bacterium is not targeted. The subject is then monitored to detect accumulation of bacterium at or in a wounded tissue or inflamed tissue inside the subject, where detection of the accumulation indicates the location of wounded tissue or inflamed tissue inside the subject, and wound or inflamed tissue is thereby detected. All pending claims are dependent upon claim 1 and, thus, include all limitations of claim 1.

Differences between the claims and the disclosure of Hamblin *et al.*

Hamblin *et al.* discloses administration of a bioluminescent strain of *E. coli* **directly into a visible incision wound on a mouse** for **"real-time monitoring of infection."** Hamblin *et al.* does **not** disclose a method of detecting wounded or inflamed tissues, but describes experiments designed to monitor infections in order to assess effectiveness of anti-

bacterial therapies, particularly photodynamic therapy (PDT). Hamblin *et al.* states on page 52, column 2:

> We report here a demonstration of proof-of- principle of PDT for infection, using a topical application of PS [photosensitizer] followed by illumination with red light to destroy bacteria infecting excisional wounds in mice, without harming the host tissue.

Thus, Hamblin *et al.* does not describe a method for detection of wounds and inflamed tissue, but describes creating wounds and infecting them with detectable bacteria in order to assess the effectiveness of PDT for killing the bacteria. This is completely different from the instant claims, which are directed to methods for **detecting wounds and inflamed tissues** inside of subjects using detectable bacteria that accumulate in the wounds and inflamed tissue and detecting the bacteria, thereby detecting wounds and inflamed tissue inside of the subject.

The instant application demonstrates and describes that bacteria and other microorganisms that replicate in the subject, are not pathogenic to the subject, are recognized by the immune system of the subject; and are not targeted to any tissue, accumulate in wounded and inflamed tissues. Because they are recognized by the immune system, the bacteria and other microorganism, when systemically administered, are cleared from most tissues, but, as described in the application, wounded and inflamed tissues are immunoprivileged. Because of this, as described in the application, the detectable microorganisms can then be used as reagents to identify wounds and inflamed tissues inside of subjects. Hamblin *et al.* does not describe or suggest systemic administration nor that upon systemic administration the microorganisms accumulate in inflamed or wounded tissues. Hamblin *et al.* does not describe any method in which the location of bacteria is employed to then locate wounds or inflamed tissue. As described above, Hamblin *et al.* is assessing the effectiveness of antimicrobial therapy and employs labeled bacteria, which were applied to the wounds, to assess whether the therapy is killing the bacteria.

Furthermore, Hamblin *et al.* does not disclose detection of wounds and inflamed tissue inside of a subject. As amended the claims clearly recite that the detected wounds and inflamed tissue are inside the subject. For administration of the bacteria, Hamblin *et al.*, describes in column 2 on page 52 that:

> Four full-thickness excisional wounds were made in a line along the dorsal surface...using surgical scissors and forceps...A suspension (50 pL PBS) containing $5x10^6$ cells of midlog phase E. coli (10^8 cells mL^{-2}) was inoculated ***into each wound***, and the mouse was imaged with luminescence to ensure equal bacterial loading into each wound. [emphasis added].

The bacteria administered to the mice express the *lux* operon from *Photohaddus luminscens* and are monitored at the wound by detection of luminescence. Hamblin *et al.* thus discloses monitoring of bacteria in a wound that has already been detected on a mouse.

Hamblin is monitoring the development of an infection in a wound **not detecting the wound**. An excisional wound is not inside the subject.

Hamblin *et al.* detects expression of the lux operon in order to control loading of the bacteria into each wound. Hence detection is for quantitating bacteria, not detecting wounds. Hamblin *al.* does not disclose *detection* of a wound *within a subject* because the bacteria are administered directly to the wound. Hence, Hamblin *et al.* does not disclose *detection* of a wounded or inflamed tissue; Hamblin *et al.* detects bacteria in order to monitor bacterial treatment. Finally Hamblin *et al.* topically applies bacteria to an exicisional wound and does not describe systemic administration. Thus, Hamblin et al. does not disclose a method for detection of a wounded or inflamed tissue, does not disclose a method that includes the steps of systemically administering bacteria, nor detecting the bacteria inside the subject, nor using the bacteria to detect the presence of inflamed or wounded tissue inside of the subject. Therefore, Hamblin *et al.* fails to disclose several elements as claimed, including a method that includes detection of a wounded or inflamed tissues. Because Hamblin *et al.* does not all elements as claimed, the reference does not anticipate claim 1, nor any dependent claim thereon.

Rebuttal to comments of the Examiner

The Examiner states that Applicant distinguishes the claimed based upon the fact that "invisible wounds" are detected. This is not correct, the distinction is that Hamblin *et al.* does not disclose a method of detecting visible or invisible wounds. Hamblin *et al.* describes a method for assessing the efficacy of anti-bacterial treatment. Hamblin *et al.* employs detectable bacteria in order to quantitate the bacteria upon administration of anti-bacterial therapy to assess whether the therapy is effective. Hamblin *et al.* does not describe any method for detecting visible or invisible wounds.

B. Rejection of Claims 1, 2, 9, 12, 18 and 22 under 35 U.S.C. §102(b)

Claims1, 2, 9, 12, 18 and 22 are rejected under 35 U.S.C. 102(b) as anticipated by Fu *et al.*, which allegedly discloses that bacterial flora of the gut can contaminate cutaneous burn wounds, as demonstrated detection of labeled *E. coli* in the burn. The Examiner states that the *E. coli* was recognized and cleared by the immune system, and thus is considered nonpathogenic, and uses the pUC19 plasmid, which encodes the antibiotic ampicillin as a therapeutic agent. The Examiner alleges that because "living bacteria were found to have reached the burn tissue after traveling through the stomach, lining of the gut, and the liver, they replicate in the subject". The Examiner continues and states that because ampicillin was

expressed, the *E. coli* are considered to comprise an inducible promoter regulating expression of ampicillin, that is, expression of ampicillin from the pUC19 vector is inducible upon introduction of the vector into a bacterial cell. This rejection respectfully is traversed.

Relevant Law

See above.

The Claims

The claims are discussed above.

Disclosure of Fu *et al.* and differences from the instant claims

Fu *et al.* is directed to a study of the role of bacteria in the gut in severe burn infections. As with Hamblin *et al.*, Fu *et al.*, does not disclose any method for detection of wounds or inflamed tissues. Fu *et al.* is detecting bacteria in order to study trafficking ob intestinal bacteria in infections following severe burns. Fu *et al.* concludes that intestinal bacteria can traffic through the damaged intestinal wall and call infections.

Fu *et al.* provides a study assessing the role that fecal organisms play in burn wound infection. To study this role, Fu *et al.* provides an animal model to observe the:

> dynamics of fecal organisms and burn wound organisms in attempts to investigate the relationship between translocation infection by fecal organisms and burn wound infection more precisely.

Thus, Fu *et al.* does not disclose or even hint at a method for detecting wounds or inflamed tissues.

To assess the role of fecal organism translocation in infecting burn wound, fluorescence labeled bacteria were introduced into Wistar rats through a gastric catheter, followed by 30% TBSA to cause third degree burns in the gut. After predetermined time periods, the rats were sacrificed and organs excised to assess bacterial infection by fluorescence. In another group of rats, bacteria containing pUC19 to provide ampicillin resistance for selection (not therapy) were inoculated into the intestines of the rats through a catheter, and fed ampicillin to select for the introduced bacteria. After confirming that the Amp-resistant bacteria were incorporated into the intestinal tract, the rats were burned, and then sacrificed and their organs harvested and bacteria cultured in medium containing ampicillin. Plasmid was extracted and identified by restriction digestion patterns.

Fu *et al.* states that the results indicate that in the early stage of a severe burn, intestinal bacteria can penetrate through the damaged intestinal membranous barrier and disperse. Thus, enterogenous infection should be considered in cases of sepsis in early burn stages.

Fu *et al.*, thus, discloses that intestinal flora can cause sepsis in severe burns. Fu *et al.* provides an animal model for studying such infections. Fu *et al.* does not disclose a method for detection of wound and inflamed tissues; Fu *et al.* is studying infection following severe burns; no detection of wounds and inflamed tissue is involved. Fu *et al.* does not disclose systemically administering detectable bacteria to a subject, and then detecting accumulation of the bacteria in order to identify the location of a wound or inflamed tissue inside of the subject. While Fu *et al.* uses detectable bacteria, the method is for detecting bacteria not detecting wounds or inflamed tissue. Fu *et al.*, thus, does not disclose all elements of claim 1 nor any claimed. Therefore, Fu *et al.* does not anticipate any pending claim.

THE REJECTION OF CLAIMS 6 AND 16 UNDER 35 U.S.C. §103(a)

Claims 6 and 16 are rejected under 35 U.S.C. 103(a) as unpatentable over Fu *et al.* in view of Welling *et al.* and Weissleder *et al.* . because, while Fu *et al.* fails to teach a method where monitoring is performed by MRI, "Weissleder *et al.* teaches that MRI imaging using proteins such as transferrin was known in the art as an alternative to optical imaging and Welling *et al*, demonstrates detectable labeling of molecules for *in vivo* use in MRI methods. The Examiner concludes that one of ordinary skill in the art would have been motivated to have substituted "MR imaging as taught by Weissleder and Welling et al for the optical imaging used in the method Fu et al." and that one of ordinary skill in the art would have expected success, sinc Fu *et al.* had demonstrated that intestinal bacteria can cause infections following severe burns. This rejection respectfully is traversed.

Relevant Law

To establish prima facie obviousness under 35 U.S.C. §103, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). This principle of U.S. law regarding obviousness was not altered by the recent Supreme Court holding in KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727, 82 USPQ2d 1385 (2007). In KSR, the Supreme Court stated that "Section 103 forbids issuance of a patent when 'the differences between the subject m*att*er sought to be patented and the prior art are such the subject m*att*er as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject m*att*er pertains.'" KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1727, 1734, 82 USPQ2d 1385, 1391 (2007).

The question of obviousness is resolved on the basis of underlying factual determinations including (1) the scope and content of the prior art, (2) any differences between the claimed subject m*att*er and the prior art, (3) the level of skill in the art. Graham v. John Deere Co., 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). See also KSR, 127 S.Ct. at 1734, 82 USPQ2d at 1391 ("While the sequence of these questions might be reordered in any particular case, the [Graham] factors continue to define the inquiry that controls.") The Court in Graham noted that evidence of secondary considerations, such as commercial success, long felt but unsolved needs, failure of others, etc., "might be utilized to give light to the circumstances surrounding the origin of the subject m*att*er sought to be patented." 383 U.S. at 18, 148 USPQ at 467. Furthermore, the Court in KSR took the opportunity to reiterate a second long-standing principle of U.S. law: that a holding of obviousness requires the fact finder (here, the Examiner), to make explicit the analysis supporting a rejection under 35 U.S.C. 103, stating that "rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. Id. at 1740-41, 82 USPQ2d at 1396 (citing In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)).

While the KSR Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. KSR, 127 S. Ct. at 1731. The court stated in dicta that, where there is a "market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try **might** show that it was obvious under § 103."

In a post-KSR decision, PharmaStem Therapeutics. Inc. v. ViaCell. Inc., 491 F.3d 1342 (Fed. Cir. 2007), the Federal Circuit stated that:

> an invention would not be invalid for obviousness if the inventor would have been motivated to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. Likewise, an invention would not be deemed obvious if all that was suggested was to explore a new technology or general approach that seemed to be a promising field of experimentation, where

> the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

Furthermore, KSR has not overruled See In re Papesch, (315 F.2d 381, 137 USPQ 43 (CCPA 1963)), In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991), and In re Deuel (51 F.3d 1552, 1558-59, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995)). "In cases involving new compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." *Takeda v. Alphapharm*, 492 F.3d 1350 (Fed. Cir. 2007).

The mere fact that prior art may be modified to produce the claimed subjected does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); see, also, *In re Papesh*, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963). In addition, if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

As always, unexpected properties must always be considered in the determination of obviousness. A compound's structure and properties are inseparable so that unexpected properties are part of the subject matter as a whole. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963)

The disclosure of the applicant cannot be used to hunt through the prior art for the claimed elements and then combine them as claimed. In re Laskowski, 871 F.2d 115, 117, 10 USPQ2d 1397, 1398 (Fed. Cir.1989). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

The rejected claim

Claim 6 recites that in the method of claim 1, the bacterium encodes a protein that induces a signal detectable by magnetic resonance imaging (MRI) or that binds to contrasting agent, chromophore or a ligand. Claim 16 is directed to a method of detecting a wound, wounded tissue or inflamed tissue or a disease associated therewith in a subject by administering a bacterium and monitoring the subject to detect the accumulation of the

bacterium at the wound, wounded tissue or inflamed tissue, where the monitoring is performed by magnetic resonance imaging (MRI).

Teachings of the cited references and differences from the claimed method

Fu *et al.*

As discussed above, Fu *et al.* fails to teach or suggest a method for detection of wounds or inflamed tissue. Fu *et al.* is directed to a study to demonstrate that intestinal bacteria can penetrate the intestinal walls following severe burns and can cause infection or contribute to infection following severe burns. Fu *et al.* detects the bacteria in wounds, but does not teach or suggest using bacteria as way to monitor a subject to detect wounds or inflamed tissues. Fu *et al.* does not teach or suggest administering bacteria to a subject to detect wounds and inflamed tissue. Fu *et al.* does not suggest that bacteria are cleared from healthy tissue but accumulate in inflamed and wounded tissue.

Fu *et al.* introduces labeled bacteria in order to mimic *in vivo* processes to assess whether intestinal bacteria can participate in infections following severe burns. Furthermore, Fu *et al.* does not show that administered bacteria accumulate in wounds and inflamed tissues rather than healthy tissues, such that they can be used as a diagnostic. There is no teaching or suggestion for administering bacteria, with the requisite properties required to achieve accumulation in wounds and inflamed tissues and clearance from healthy tissue, as a diagnostic reagent to detect wounds and inflamed tissues. Fu *et al.* uses labeled bacteria to follow their trafficking throughout a model organism and does not show that they accumulate only in wounds and inflamed tissue nor to detect wounded or inflamed tissues. The bacteria are labeled in order to show that they participate in infection. Therefore, Fu *et al.* is irrelevant to any of the pending claims and does not teach any elements of the instantly claimed method.

Weissleder *ct al.* and Wells *et al.*

Neither Weissleder *et al.* nor Wells *et al.* teach or suggest a method for detecting inflamed or wound tissue. Thus, they cannot cure the deficiencies in the teachings of Fu *et al.* Neither references teaches or suggests a method for detecting a wounded or inflamed tissue, and neither suggests a method for detecting or imaging wounds or inflamed tissue by administering bacteria. Neither reference suggests that bacteria can accumulate in wounds and inflamed tissues in order to detect and distinguish such tissues from non-wounded/inflamed tissues.

Analysis

The combination of teachings of Fu *et al.*, Wells *et al.*, and Weissleder *et al.* does not result in the instantly claimed methods

The instant claims are directed to a method of detecting a wounded or inflamed tissue inside a subject by administering bacteria to a subject in whom the presence or absence of wound is to be detected. Fu *et al.* is directed to a study of the role of intestinal bacteria in infection following sever bourns. There is no teaching or suggestion of for detecting any wounded or inflamed tissue within a subject via administration of a bacterium nor a showing that systemically administered bacteria with the recited properties accumulate in wounds and inflamed tissues inside a subject. Neither Wells *et al.* nor Weissleder *et al.*, singly or in any combination cures these deficiencies.

Furthermore, there is not teaching or suggestion in either reference to do that which applicant has done (In re Fritch). No art of record teaches or suggests that bacteria having the recited properties accumulate in wounds or inflamed tissues within a subject. Thus, there is no teaching or suggestion to do that which applicant has done.

Therefore, the combination of teachings of the references does not result in the instantly claimed methods. The Examiner has failed to set forth a *prima facie* case of obviousness.

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In view of the above, reconsideration and allowance of the application respectfully are requested.

Respectfully submitted,

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